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DESCRIBING THE BURDEN OF MALARIA ON CHILD DEVELOPMENT: WHAT SHOULD WE BE MEASURING AND HOW SHOULD WE BE MEASURING IT?

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Abstract. There are a number of pathways, both direct and indirect, through which malaria infection could impact the course of child development, causing impairment and disability and adding to the burden of malaria. We present an overview of relevant studies that illustrate these pathways, updating the evidence previously presented. We conclude that before the mechanisms and numbers of affected children can be adequately defined, a wider range of potential pathways to impaired development need to be investigated. Only then can the calculation of the burden be evidence-based, rather than merely speculative. Priorities for future research are described. The calculation of the impact of malaria on child development also requires a degree of uniformity in the definition of outcome across studies. This is currently lacking, and suggestions are made for a common approach to the reporting of results.

INTRODUCTION

New data looking at the association between malaria infection and learning in childhood reflect the growing recognition of the importance of the growth and development burden of malaria (Carter J, unpublished data).[1–3] There are still very few studies on this, and possible pathways remain under-investigated. In addition, there is a wide variability in the methodology applied to measure developmental outcome, constraining the way in which the results from different studies can be combined to form general conclusions. Much of this variability is inherent for, unlike outcome measures such as death and disease rates, measures of development need to vary across ages, sex, and cultural and linguistic groups to maintain their appropriateness for each group. Just as a child three years old cannot complete the same tasks as a 10-year old, the content of tasks and questionnaires needs to differ between cultural groups according to the images, words, and materials that are familiar to the population being tested. The way children respond to questions posed by adults also varies markedly from one community to another, necessitating changes in procedure. Furthermore, there is little cross-cultural experimental work on test validity, so that even when the same tool is used, no assumptions can be made that the same neuropsychologic function is being measured.[4,5]

To overcome these inherent differences in the data, we suggest applying "The International Classification of Functioning, Disability and Health" (ICF)[6] to combine within one framework the outcomes identified from different studies. We have used the evidence of recently published studies to update our previous description of the pathways to impairment.[7] This overview has been used to identify important topics for future research (what should we be measuring?) and to highlight methodologic issues that need to be addressed in future studies (how should we be measuring it?). Answers to these two questions are important in the identification of priority areas for intervention to reduce the burden of malaria on child growth and development.

CLASSIFICATION OF IMPAIRMENTS

The first tier of the ICF is "Impairment of Body Functions and Body Structures." Impairment is defined as a significant deviation or loss of body function or structure in the functional areas summarized in Figure 1. Classification should be by category of function and degree of impairment. Each category label given in Figure 1 is further sub-divided. For example, mental functions divide into consciousness, orientation, sleep, attention, memory, intellectual, language, energy and drive, emotional, perceptual, and higher-level cognitive functions. Movement-related functions include mobility of joints, muscle power, muscle tone, and involuntary movements. Analysis at the level of impairment can provide information on the causal pathways of disability and the degree of impairment. However, to apply this first tier at its most detailed level requires tools with sufficient sensitivity to define impaired performance as well as an understanding of what these tools are actually measuring (e.g., motivation/attention or intellectual function). In the majority of cases, the manner in which assessments are currently reported limits the ability to draw conclusions at any but the most general level.

The second tier, also summarized in the same figure, is "Activity Limitations and Participation Restriction." This refers to the implications of an identified impairment, or disability. To apply the second tier an assessment needs to be made of the ability of an individual to lead a normal life. Knowledge of parental perceptions of a child's difficulties, and of community expectations is essential to make an evaluation of disability. Saying that the child's memory, speech, or gait is impaired without reference to the context in which the child lives is not sufficient to understand the impact on their functioning in everyday living. In practice, access to the ethnologic knowledge required to make this evaluation is limited, either because it has not been published alongside research data or, more commonly, because it has not been collected. Research needs to accord greater importance to evaluating the ability of children to meet the demands of everyday living before there is sufficient data to complete the "Activity Limitations and Participation Restriction" tier. Our summary will therefore be restricted to classification at the first tier of the ICF.

Pathways to impairment. Figure 2 shows the proposed pathways to impaired development. It takes a random sample of 1,000 children and young people from a mesoendemic transmission area, approximately 50% of which will test positive for malaria parasites. Four hundred of them will have an asymptomatic infection, 98 will have symptomatic infection of a mild nature, and only 2 will have severe disease. The figure also shows that there are a number of potential pathways,

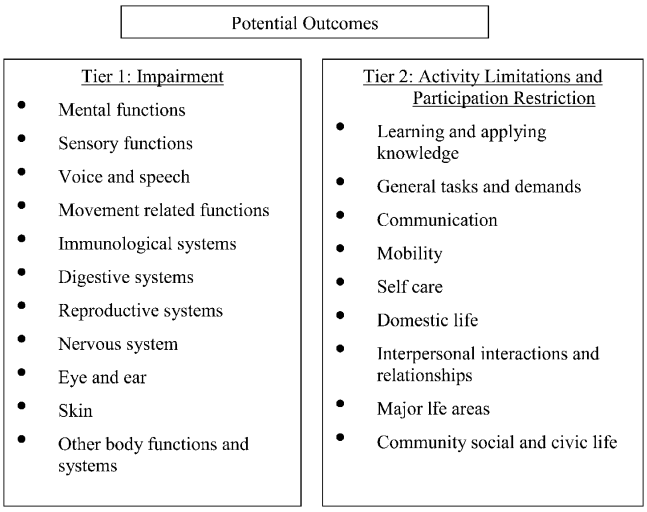

FIGURE 1. Summary of the International Classification of Functioning, Disability, and Health.[6]

both direct and indirect, from malaria parasite to impaired development. We describe the evidence for impaired outcome for each potential pathway and use the ICF classification to summarize the associated categories of impairment. For some potential pathways we have had to draw inferences from the literature on related diseases. The outcomes are listed in Table 1.

REVIEW OF RESEARCH

Presence of parasites. The investigation of impaired development in relation to parasite load has largely been limited to exposure *in utero*. The focus has been on the indirect effect of placental parasitemia on birth outcome, which is discussed in more detail in the section on fetal growth.

In school age children investigations have focused on the effect of parasite clearance on fine motor skills, cognition, physical growth and school achievement.[7–10] With a limited number of studies to draw from, our conclusions are tentative, but suggest that the association varies by age and level of transmission. Short-term parasite clearance has been associated with improved performance on fine motor and memory tasks.[1] The mechanism for impairment is not clear, but may be through an alteration of attention levels.[11] Longer-term follow-up is needed to establish whether benefits can be maintained over time. However, the cost of extended intervention programs and the associated risks of the development of drug resistance suggests that selecting school age children as targets for chemoprophylaxis has limited efficacy.[12] The benefits of other methods of controlling the parasite burden, such as the use of insecticide-treated bed nets, have not yet been investigated.

Of greater interest are the potential benefits of reducing the parasite burden in the first few years of life on later physical growth and the development of mental functions. The early years are critical for brain growth and the potential benefits of intervention at this vulnerable time may come from having a more attentive and alert child[11,13] and from avoiding exposure to brain insult and the associated risk of developing neurocognitive sequelae. Data on the relationship between exposure to parasites in the early years and later development have yet to be published. However, exposure is also important for the development of functional immunity to malarial disease, and the potential shortcomings of delaying this process are discussed.

Mild malaria and the activation of an immune response. The effect of mild disease on later development is yet to be investigated. Potential outcomes are suggested by the association of other mild diseases with the activation of the immune response system, suppression of appetite, and reduction in the speed of reaction time (the speed at which decisions and responses are made).[14] However, these effects are likely to be very short term. There may be a longer- term effect on activity and participation if a child experiences regular episodes of mild disease. To evaluate the longer-term risk, we need to take into account the contribution to outcome of the number and length of periods of ill health as well as the age at onset of disease episodes.

We have already suggested that school age children may not be an important target group for preventative intervention programs. This is supported by data from treatment programs aimed at reducing absence from school, which have shown limited impact on attendance levels and disease incidence.[15,16] Programs with specific targets within the school-age population may have more visible benefits. In endemic areas episodes of malaria disease account for about 3–8% of all absences and prompt treatment may reduce this by half.[12] There is growing evidence that school-based treatment programs supervised by teachers can have a significant effect on reducing the burden of malarial disease in school children.[17,18] In regions of highly seasonal or epidemic malaria, preventative intervention programs initiated early in the malaria season could significantly reduce the risk of developing severe disease.[19]

The overwhelming burden of disease, both mild and severe, is carried by children less than five years old. Intervention studies aimed at reducing the burden in this age group need to evaluate the potential benefits in improved growth and development against the potential risk that they are simply changing the age profile of disease through delayed development of natural immunity.[20] Current data provide mixed evidence, and longer-term follow-ups, in particular, are needed (Eisele TP and others, unpublished data).[21] Until the relationship between early protection and the development of natural immunity is better understood, it would be prudent to continue to monitor for the possibility of changes in disease profile.

Severe disease and brain damage. Of the two major manifestations of severe disease, severe malarial anemia and cerebral malaria, it is only the association between cerebral malaria and impaired growth that has been investigated. Gross neurologic sequelae on discharge have been widely documented (see summary in the report by Holding and Snow[7]). There have been some studies of neuropsychologic consequences (Carter J, unpublished data, Dugbartey AT, unpublished data)[3,22–24] one which concluded that there were no long-term sequelae. However, the weight of the evidence suggests that, in common with other childhood encephalopathies, the more severe the illness the more generalized and long term are the impairments.[25] Using the ICF[6] to summarize the results across these studies, impairments in two functional areas, attention[1,20,22] and motor development,[22,23] are

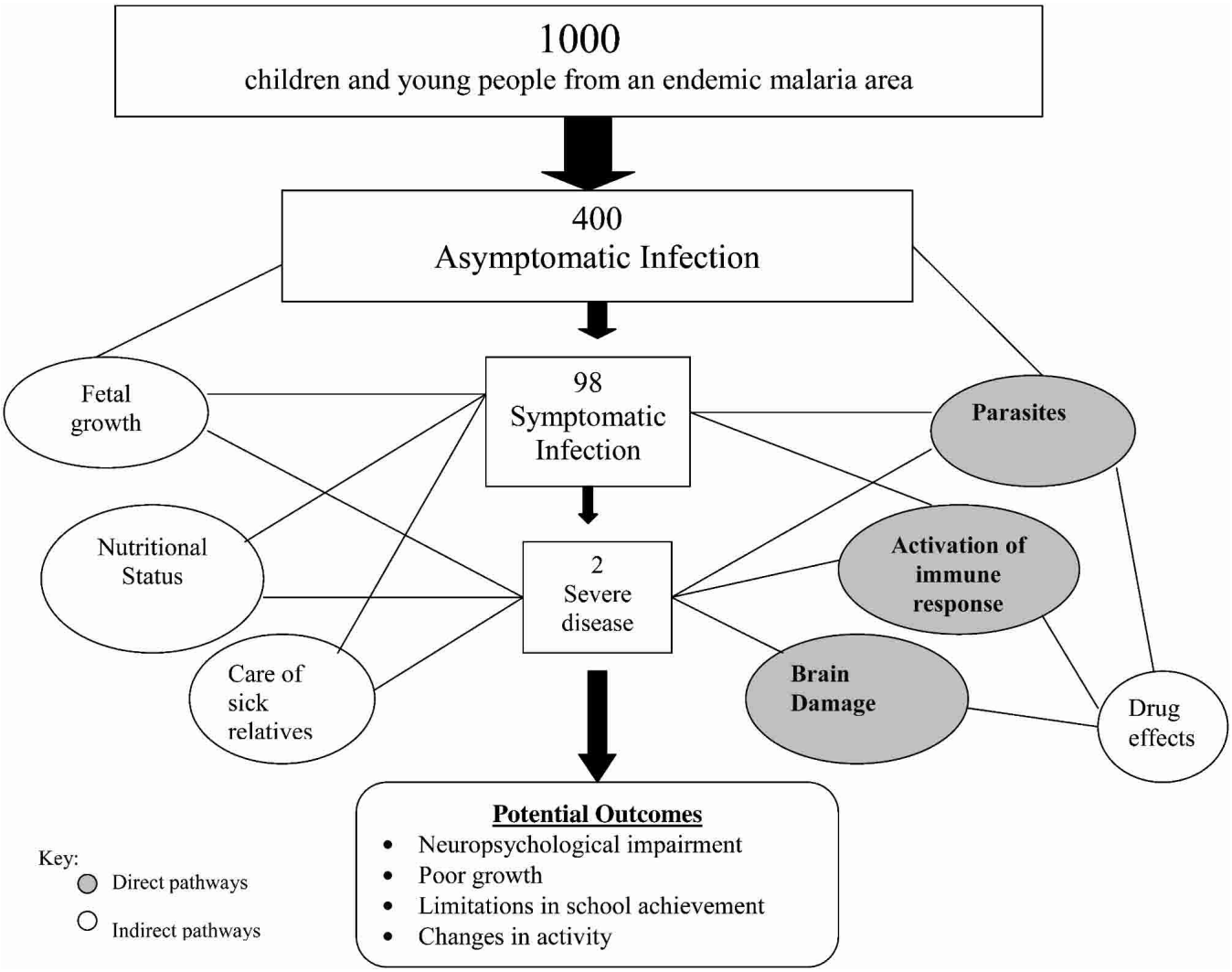

FIGURE 2. Proposed direct and indirect pathways to impaired development.

identified as the more common sequelae, and future investigations should monitor performance in these areas.

The variability in outcome observed both between and within studies needs explaining. Differing methodologies and differing inclusion criteria in the selection of subjects contribute to the variability found between studies. Variability in outcome between subjects will be as a consequence of a number of factors, and, an understanding of the relative contribution of each is important to planning future interventions. One such factor is age at insult. The exact function(s) that are impaired may depend on the stage of brain growth at which the insult is encountered.[26,27] Impairment may be attributable either to identifiable lesions, or to the subsequent interference in the development of neuronal systems in the brain. Complex, higher order functions, which require more intricate systems, may be more vulnerable, but impairment may not be manifest until the child is older. A detailed study of the relationship between age of insult and outcome, which may be able to tease out some of these issues, is yet to be carried out.

TABLE 1
Summary of observed and inferred impairments by pathway after applying the ICF*

	Impairment Classification								
Pathway to impairment	Mental	Sensory	Voice/Speech	Movement	Immunological	Digestive	Reproductive	Nervous	Eye/Ear
Parasitization	1			1		2,3,8,9			
Mild malaria	x					x			
Severe disease	2,22–24*	24	4	23,24				7,24	47
Caring for the sick	x								
Nutrition	x	47	72	102	12,35–39			x	
Fetal exposure	x	x		x	x	74–78			
Anti-malarials					x		x	x	

* Carter J, unpublished data, Dugbartey AT, unpublished data.
Impairments inferred from related literature are shown by an 'x'.

Another explanation for the variability observed may be that several studies have used different methods for developing case definitions of cerebral malaria, and the term has been used to combine children who have experienced different pathophysiologic mechanisms. The investigation of one potential sub-group, children with malaria and seizures, indicates that severe impairment can follow less severe disease when underlying brain pathology (i.e., epileptic activity) continues beyond the illness episode.[3] Identifying other sub-groups whose symptoms places them within the syndrome of 'cerebral malaria' is a priority for the greater understanding of sources of variability in outcome. Other possible defining symptoms are episodes of severe hypoglycemia, and the failure to mount a high fever.[24]

Contributing to variability in outcome will also be the other risk factors that individual children encounter. Some risk factors may have a synergistic relationship with malarial disease, while other variables may provide protection against severe sequelae. Maternal literacy, for example, has beneficial effects on children's general health and well being.[28] While school attendance is associated with superior performance on neuropsychological tests (Holding P, unpublished data), the difference between schooled and unschooled children has been found to be even greater in those who have experienced cerebral malaria compared with those who have not.[29] One causal factor might be that education contributes to resilience in the face of adverse experiences.[30] The inter-relationship between risk factors and factors which might attenuate those risks is itself complex.[31] An understanding of this relationship is important in calculating the persistence of impairment, and in planning successful intervention programs.

Care of sick individuals. Malarial disease in the family may reduce access to education and thus future employment opportunities for children who are not themselves infected. It is not known how much of the 92% plus of school days lost to causes other than direct malaria infection are spent taking care of sick siblings.[12] The temporary interruption of school attendance may disrupt the development of literacy skills. Schooling may cease altogether due to the financial burden of treatment costs for sick individuals thereby severely limiting the family's ability to support the continued education of all its eligible members.[32–34]

Nutritional status and malarial infection. Infection with both *Plasmodium falciparum* and *P. vivax* has been associated with impaired physical growth in children.[35–39] The direction of this association appears to be two-way, with malaria leading to compromised nutritional status and compromised nutritional status increasing susceptibility to malaria infection. Catch-up growth has been observed following interventions focusing on disease prevention,[9] suggesting that malaria infection plays a role in the etiology of malnutrition, and the downward cycle of impaired development of mental functions.[40,41] The role of poor nutritional status in the etiology of severe malarial disease needs further clarification. The major limitation of investigations, particularly the earlier ones, is the categorical (rather than dose-response) design of the study. Later studies suggest that variability in outcome is to be expected due to differing relationships between differing levels and types of nutritional deficits, combinations of health risk factors and age at time of study. Hospital-based studies have suggested that protein energy malnutrition may be protective against malaria-related morbidity and mortality.[42–44] There is increasing evidence from larger community-based studies that a compromised diet at both the macronutrient and micronutrient level may actually increase the risk of developing disease and/or a range of impaired outcomes.[45–48] The debate continues, with more recent counter-evidence to the picture of a synergistic relationship between malarial disease and malnutrition showing an apparent protective effect of stunting[49] and low body mass index.[50]

Although the relationship between nutritional status and malaria infection is complex, the nature of the relationship can be reduced to two essential pathways: the modulation of the immune system and alterations to oxidative stress. Investigations of the relationship between nutritional status and malarial disease have concentrated on those nutrients that may have a significant impact on either pathway, such as vitamin A, zinc, and protein. Deficiencies in these nutrients may also directly impact on the growth and development burden, as evidenced by the benefits of supplementation of children's diets with vitamin A, zinc, and protein-rich foods on performance in mental functions, social and emotional development, and physical growth.[51–55]

The role of iron is more contentious, both in relation to malaria infection, and to impaired cognition.[56–61] A significant association has been established between malaria infection and the development of anemia,[62,63] although not iron-deficiency anemia. Since it is specifically iron-deficiency anemia that has been associated with impaired mental functions,[64–68] the same association may not be seen with malarial anemia. Iron supplementation of a malaria-exposed population may still have a role to play in reducing the burden of malaria disease, if careful account is taken of the particular combination of disease risk to which the population is exposed.[57,69–71] This premise holds true for other areas of nutrition.[72]

There is a growing body of evidence, carefully summarized by Shankar[72] and Nussenblatt and Semba,[73] supporting those who advocate combination therapies of micronutrient and macronutrient supplementation and anti-malarials for the treatment and prevention of mild and severe disease. Again, the potential benefits appear to vary depending upon the age and immune status of the population being studied, and the level and nature of the nutritional deficit.

Fetal exposure to malaria. Maternal malaria infection in pregnancy has a well-documented association with impaired outcome for the fetus, including intrauterine growth retardation and premature delivery, both culminating in low birth weight.[74–78] Uterine placental insufficiency in non-malarial populations has been associated with the etiology of cerebral palsy, and with white matter damage.[79–81] Compromised fetal growth is therefore associated with impaired development of the central nervous system, and subsequent impairment of mental, motor and sensory functions.[79,82] Impairment can be experienced by the whole range of low birth weight children (< 750–2,500 grams)[83,84] and can persist into adulthood.[85,86] Further evidence suggests that impairments in cardiovascular and respiratory structures may also have long-term health implications for these children.[87]

Sub-optimal growth and development may also result from a combination of risks. For example, the risk of low birth weight is significantly increased by the co-existence of malaria infection and maternal anemia.[88] The children born to these mothers are also at risk of fetal anemia.[76] Fetal growth retar-

dation might not be the only pathway to impairment. Another mechanism for poor outcome might be intrauterine infection. Placental cytokine changes have been recorded with maternal malaria infection.[89] When a fetal inflammatory response, with corresponding changes in cytokine levels in amniotic fluid or newborn blood, is stimulated, then brain damage and neurodevelopmental disability in the child may follow.[82,90] Congenital malaria, which may be a more direct pathway to impairment, is thought to be relatively uncommon.[88] However, peripheral parasitemia, which is significantly associated with anemia in infancy, has been recorded in 42% of newborns tested.[89] It is further suggested that pre-natal exposure to malaria parasites may be related to retarded development of natural immunity.[90] The most vulnerable are the children of primigravidae, since more than 60% of their mothers will have been infected with malaria.[77,88] With more than two million babies born with low birth weight in sub-Saharan Africa every year, and with estimates of malaria accounting for up to 40% of these births,[91] this pathway to impairment is potentially a major contributor to the burden of malaria disease and may ultimately lead to long-lasting and wide reaching limitations in daily living.

Effects of anti-malarial drugs. Another potential indirect source of impaired functioning is the effect of the anti-malarial drugs themselves. While the clinical application of these drugs has been widely studied, research provides little information on possible negative effects on performance, especially following extended use. An investigation of the effect of the temporary prescription of chemoprophylaxis on psychomotor performance in adults found no adverse effects.[92] We found no published data on the effects of the use of anti-malarial drugs over a prolonged period of time by either children or adults permanently resident in malaria endemic areas. It may be that the prohibitive cost of such regimens for the majority reduces the potential burden of this pathway to impairment. However, until there are studies of prolonged usage we should remain cautious about drawing a firm conclusion about either the association of anti-malarial drugs with impairment, or the size of the potential burden.

The use of antimalarial regimens in pregnancy has been more widely studied, although the teratogenic effect on the fetus has not been specifically investigated for all drugs available. A very careful evaluation of the data has recently been published by Newman and others.[93] Outcomes discussed include birth outcomes, birth defects, and the risk during lactation. They conclude that intermittent presumptive treatment with sulfadoxine-pyrimethamine (SP) provides the most effective protection against the risks of malaria in pregnancy. Concerns derived from literature on illnesses other than malaria that sulfonamides may increase the risk of birth defects and kerniticus,[94,95] have not been supported by studies of the use of SP in mid and late pregnancy. However, caution is recommended about the use of anti-malarials in the first trimester and while breastfeeding premature and ill babies.[96]

Our conclusion is that there is a risk of an association between the extended use of anti-malarials and impaired outcome, but that further investigation is required to evaluate the nature and extent of that risk. Furthermore, it is likely that the risk will vary significantly depending upon the specific population being investigated. Even when the data is collected no one general conclusion is likely to explain all the results.

DISCUSSION

Both direct and indirect exposure to malaria leads to impairment and disability, and the effects extend beyond the time of infection.[1,2,22,24] This relationship holds true at varying levels of severity of infection, although in general, the sicker the child the higher the risk of developing more severe, longer term impairment.[22,24] At the more severe level of impairment, a small, but not insignificant number of children are implicated. Much larger numbers are at risk of impaired development through one of the indirect pathways described. For all pathways, the implication is that the level of risk changes with different combinations of other health and environmental risks. Despite the differences in the assessment tools applied in the reported studies, the application of the ICF has helped to summarize results across different contexts, and to clarify which functional areas are more commonly implicated in the literature.

Our understanding of the burden of malaria on growth and development still remains speculative, and future studies need to report outcome in a manner that allows evaluation of the level of impairment and its impact on daily living. The most common impairments observed are of movement-related functions, mental functions, and the digestive system (weight maintenance). Other outcomes which have been observed are impairments of the voice and speech, reproductive functions, sensory functions, immunologic systems, and the structure of the eye. All the potential pathways described require further clarification before we can calculate either the severity of the burden or the numbers of individuals implicated.

Investigations to date have concentrated on those children who have experienced cerebral malaria and are therefore at risk of the most severe impairment. While the potential severity of the outcome supports the importance of more detailed investigations of this pathway, the total number of affected children is relatively small (1–2% of the child population in a malaria-endemic area have this form of the disease).[97] The other pathways described involve a far greater proportion of the population. The most important in terms of numbers is parasitization, where 100% of the children in endemic areas are affected. However, the effects of the parasitization may be negligible,[8] or, as suggested by the experience of macroparasitic infections, readily reversible.[98]

There is also a potential burden felt by the child who is not ill. Since this burden is disproportionately felt by those with the lowest income,[99] it might be best characterized as due to poverty rather than malaria *per se*. However, as described by Sachs and Malaney,[100] the two may be inextricably interlinked.

The literature suggests that to adequately describe the relationship between malaria and malnutrition, and to plan appropriate interventions, account must be taken of the specific and possibly changing needs of a defined target population.[101–103] The absence of data on the longer-term effects on growth and development of this combination of risk factors needs to be addressed.

The consequence of pre-natal exposure to malaria is identified as another major priority for future research, not least because of the potential size of the affected group.[104] The associated low birth weight may be a direct cause of impaired growth and development.[84] In addition, growth retardation at

this sensitive point in development may also predispose the child to adverse consequences following exposure to other risk factors.[105]

In this report, we have been primarily concerned with clarifying a description of the burden of malarial disease. We have also suggested that a single malaria infection may not itself lead to impaired outcome, but may predispose the affected child to adverse sequelae following repeated exposure, particularly when that child is challenged with a number of health risks.[106] Testing this hypothesis requires a longitudinal design.[107,108] The starting point for this analysis will need to be the first point at which the child may be exposed to malaria infection *in utero*.

The ability to quantify the problem has been severely limited not only by the paucity of studies, but also by the way in which outcome has so far been measured. To define with greater precision the severity of the impairment, and to calculate the long-term burden on individuals, their families and the wider community, a number of methodologic issues need to be addressed in future studies. The first issue concerns the selection of measurement tools applied, and the interpretation of results. The problem extends beyond needing more context-appropriate assessments.[109] Test developers need also to address the current limitation of neuropsychologic assessment, that real life implications of impaired performance are seldom defined.[110] In this overview, we were unable to apply the second tier of the ICF, "Activity Limitations and Participation Restriction," because of the absence of this information in relation to malaria infection. Descriptions of disability and of real life outcomes would help in defining the severity of the impairment observed, and in combining data across studies. Being able to define the meaning of impaired performance on tests of function in real life situations would also inform and guide support services in designing appropriate interventions.

Another limitation of the current literature arises from the cross-sectional design of the studies reported. Such studies can inform us as to the nature and extent of the burden at one age, or at one time point, post-infection. However, since child development is a dynamic process, it is best investigated in longitudinal studies.[111] A longitudinal perspective allows the description of changes in the burden as a child grows older, and is expected to play different roles in the family and community structure.[112] In some functional areas, it has been seen that the burden may decrease.[113] The study by van Hensbroek and others[113] illustrated how even dramatic neurologic impairments following cerebral malaria resolve over time, reducing the burden estimated by cross-sectional data.[114,115] Other studies have suggested that the burden of severe disease may increase with time since insult. For example, in planning and organizational skills, which do not themselves mature until after the peak incidence period for severe disease, we might expect to find an increased burden as the child grows older.[24] Longitudinal data with follow-up into adulthood is needed to evaluate both the persistence of deficits (and thus the longer term burden) and to identify the most vulnerable.

It would be inaccurate to calculate the burden of malaria on child development without taking into account the large number of potential moderators influencing variability in outcome.[116] This variability has been associated with differences in socioeconomic status and the presence of other infections and disease.[1] Differences in outcome are also likely to be a consequence of the age at which the malaria infection occurs, and the age at which outcome is measured.[117] Understanding the sources of this variability clarifies the causes of impairment, and helps to identify the malaria attributable burden.[110,116] It also helps to identify those children most at risk of persistent deficits, as well as potential entry points for intervention. Statistical procedures that can specify causal relationships between a number of observed variables such as path analysis and structural equation modeling need to be applied. Structural Equation Modeling[118] is a statistical technique designed to help isolate the individual contribution of one risk from many, as well as changes in effect following different combinations of risk. This has rarely been done in the context of malaria research,[1] and not with the size of sample from which more robust conclusions can be drawn. The study of limited series, mainly hospital-based samples, may also have given us a distorted idea of who are the most vulnerable in the population. This is illustrated by the contradictory results reported on the relationship between malaria and malnutrition in smaller, hospital-based studies compared with larger, community-based studies.[42,45,48]

The contradictions may also reflect the different risk combinations encountered.[72,73] Indeed, the multiple risk environments that characterize the lives of many children growing up in the malaria-exposed world may make it very difficult, if not impossible, to isolate the malaria attributable proportion of observed impairments.[108] It may be more meaningful to identify common partnerships of risk factors and to calculate the combined burden.[106] A combination of different intervention strategies might also be expected to have an impact greater than the sum of their separate effects.[119] In this way, interventions may be targeted at the most vulnerable.

The main conclusion that we draw from this overview is that a complex inter-relationship exists between malaria infection and a large number of other risk factors, which themselves are associated with impaired growth and development. The presence of multiple risks, and the potentially changing relationship between those risks as a child matures, makes calculating a malaria-attributable burden an extremely complex task. We suggest that it is not only more research that is required, but also a radical change in methodologic approach. Sample sizes should reflect the need to incorporate multiple potential moderators and mediators. Data should be collected across more than one time point, to allow the investigation of the role of intervening variables, and to evaluate continuity and discontinuity in development associated with malaria infection. And finally, and most importantly, measures of development used need to be more transparent. More clarity is required about what they are actually measuring, the level of impairment being measured, and what this means for the affected individual. Only then will we be able to provide data that describe the severity of the burden in terms that are directly meaningful to the affected population, comparable across populations, and show how the burden changes over time. The need for intervention is great. However, without the support of an accurate estimation of the numbers involved, it will be difficult to convince the relevant authorities to assign resources to ameliorate the burden.

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